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BRIEF REPORTS

Phase I Trial of Procarbazine as a 5-Day Continuous Infusion in Children With Central Nervous System Tumors[1]

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Seven children with previously treated brain tumors were enrolled in a phase I trial of 5-day continuous-infusion procarbazine at 360, 480, and 638 mg/m^2/day. Vitamin B_6 levels were monitored. Myelosuppression was moderate though occasionally delayed, and nausea and vomiting were mild. At the highest dose level, a patient experienced severe psychosis that persisted for several weeks. From that dose-limiting toxicity and the degree of myelosuppression, the recommended dose for phase II trials in children is the same as for adults, 450 mg/m^2/day. [Cancer Treat Rep 71:973-974, 1987]

Procarbazine has shown antineoplastic activity when tested in a variety of tumors as a single agent and in combination with other drugs. Procarbazine has been widely used in combination with mechlorethamine, vincristine sulfate, and prednisone (MOPP) to treat children with Hodgkin's disease (1). The MOPP regimen has also been effective in salvage therapy of children with brain tumors (2) as well as in primary therapy for infants with brain tumors (3). A Pediatric Oncology Group study comparing MOPP with the same regimen without mechlorethamine showed that mechlorethamine does contribute to the remission rate, even though the overall survival rate was not different (4). This discrepancy was largely due to higher toxicity in the mustard-containing regimen. The significant effect of vincristine, procarbazine, and prednisone together underscores the point that vincristine and procarbazine are active against brain tumors. The oral dose of procarbazine has been 100 mg/m^2/day $\times$ 10 in MOPP therapy, and its toxicity at this dose level has been tolerable.

The recent availability of procarbazine in an iv form made this drug a natural candidate for evaluation. However, the maximum tolerated dose of iv-administered procarbazine had not yet been determined by a phase I study in children. This study reports on one such effort. An adult phase I study recommended a starting dose of 450 mg/m^2/day $\times$ 5 days (5). Reported central nervous system (CNS) toxicity has been said to be related to vitamin B_6 depletion.

PATIENTS AND METHODS

Procarbazine was administered under a protocol approved by our Institutional Review Board. Written informed consent was obtained. All children with recurrent brain tumors who were not candidates for known effective regimens were eligible. Computed tomographic (CT) scan diagnosis was acceptable for inoperable lesions. Patients had to be well nourished and life expectancy had to be sufficient for at least one complete course with 3 weeks of observation.

Procarbazine was given iv by continuous infusion for 5 days, each 12-hour period in up to 250 ml of appropriate iv solutions, protected from light. The starting dose for these children was based on 80% of the adult starting dose. The first three patients received 360 mg/m^2/day. This dose was escalated for the next three patients to 480 mg/m^2/day. The highest dose tested was 638 mg/m^2/day. Escalation in the same patient was allowed after two doses at the level of enrollment. Doses were to be postponed if the patient had an absolute granulocyte count < 2000/mm^3 or a platelet count $< 100{,}000$/mm^3 when the next dose was due. Patients were monitored with a cbc plus differential count, liver and renal function tests, coagulation profile, serum electrolytes, urinalysis, and serum vitamin B_6 levels. All patients received a tyramine-free diet. Pediatric Oncology Group toxicity scales were used to rate toxicity (6). Tumor response was gauged by appropriate radiologi-

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TABLE 1.—Patient characteristics

Patient No.	Age*	Sex	Diagnosis	Prior therapy†	Response‡
1	8 yrs, 3 mos	M	Brainstem glioma	Surgery, radiotherapy, carmustine, MOPP	PD
2	11 yrs	M	Choriocarcinoma	Surgery, radiotherapy, CVB, CISCA/VB, VAC, HMTX	PD
3	8 yrs, 4 mos	F	Brainstem glioma	Biopsy, radiotherapy	PD
4	9 yrs, 4 mos	F	Anaplastic astrocytoma	Surgery, radiotherapy, MOPP	PD
5	10 yrs, 2 mos	F	Ependymoma	Surgery, radiotherapy	PD
6	11 mos	M	Medulloblastoma	Surgery × 2, MOPP, radiotherapy, CAPT	PD
7	6 yrs, 6 mos	F	Brainstem glioma	Radiotherapy, CAPT	SD

*Age is at time of registration.

†MOPP = mechlorethamine, vincristine, prednisone, and oral procarbazine; CVB = cisplatin and vinblastine sulfate hydrate; CISCA/VB = cisplatin, cyclophosphamide, doxorubicin, vinblastine sulfate hydrate; VAC = vincristine, dactinomycin, cyclophosphamide; HMTX = high-dose methotrexate; CAPT = carboplatin.

‡SD = stable disease; PD = progressive disease.

cal measures, usually CT with and without contrast and, in selected instances, by magnetic resonance imaging. No concurrent tumor-directed therapy was given except dexamethasone when clinically indicated.

RESULTS AND DISCUSSION

Seven patients were enrolled, two of whom advanced in dose. A total of five courses were given at 360 mg/m^2, five at 480 mg/m^2, and two at 638 mg/m^2. Patient characteristics are shown in table 1. One patient (No. 7) showed radiographically stable disease and neurological improvement after therapy. The remainder had progressive disease.

Nausea and vomiting was mild, never exceeded grade 2, and abated over a 5-day course. Myelosuppression was moderate, though it was delayed until Day 41 in one patient. All others recovered their counts by the time the next course was due. Grade III granulocytopenia occurred in one of five courses at 360 mg/m^2 and two of five courses at 480 mg/m^2. Grade III thrombocytopenia occurred in one of five courses at each of those dose levels. No life-threatening myelosuppression was seen and no infections occurred during times of granulocytopenia.

One patient, 24 hours after completion of the infusion at the highest dose, experienced an acute psychosis manifested by hallucinations, self-mutilation, and panic attacks, and required hospitalization. The serum vitamin B_6 level was normal, and vitamin B_6 administration had no effect. She was intolerant of very low doses of Thorazine and continued to have psychological sequelae. This constituted a severe, dose-limiting toxicity. At that same dose level, thrombocytopenia (< 100,000 cells/mm^3), which resolved, was seen in Patient 6. This patient was an infant who was restless for 2 weeks following completion of the infusion. In a parallel study of adults with gliomas, two of 14 patients had reversible confusion and excitation during procarbazine infusion (W. K. A. Yung, personal communication).

We conclude that the maximum tolerated dose for iv procarbazine administered in this fashion is 480 mg/m^2/day. Since that is close to the adult dose, we would recommend use of 450 mg/m^2/day if further studies are undertaken. The occasional delayed myelosuppression would probably make a schedule for children of every 4 weeks more prudent than the recommended frequency for adults of every 3 weeks.

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